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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ENZO BIOCHEM, INC.
527 MADISON AVENUE (9TH FLOOR)
NEW YORK, NY 10022

EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/693,481	RABBANI ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *251-287 and 625* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *251-287 and 625* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 18, 2008 has been entered. Claims 251-287 and 625 are currently pending and are addressed herein.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 09/896,897, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The earlier-filed '897 application does not provide

adequate support for claims 251-287 and 625 of the instant application, because it does not teach primer extension using primers containing 3' terminal nucleotides that comprise nucleotide analogues with substitutions on the 2' position of the ribose ring. Accordingly, claims 251-287 and 625 have not been accorded benefit of the earlier-filed '897 application, and the instant application filing date (October 24, 2003) has been used for prior art purposes.

Information Disclosure Statement

3. The information disclosure statement filed on September 18, 2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Specifically, references 20-25, 42-47, 50, and 51 have not been considered, because a copy of these foreign patent documents or non-patent literature publications has not been provided.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 251-264, 269-273, 275, 281-286, and 625 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1 201 768 A2; cited previously).

Lin teaches methods for generating cDNA libraries from cells (see Figure 1 and column 2, line 42 – column 3, line 16).

Regarding claims 251, 264, and 281, Lin teaches a method for synthesizing one or more copies of a library of target nucleic acids comprising:

(a) providing:

(i) a library of target RNA molecules (col. 6, lines 10-17 and col. 2, lines 45-51; see also Figure 1, step a)

(ii) primers comprising sequences complementary to homopolymeric sequences in the library of nucleic acid targets (see Figure 1, column 2, lines 52-56, column 6, lines 17-21 and lines 60-65)

(iii) synthesizing reagents for the synthesis of a nucleic acid copy (column 2, lines 52-55 and column 6, lines 15-24)

(iv) addition reagents for addition of a non-inherent universal detection target (UDT) comprising terminal deoxynuclsotidyl transferase (TdT) (column 2, lines 58-65 and column 6, lines 25-32)

(b) annealing the primers to the homopolymeric sequences in the library of target nucleic acids (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21)

(c) extending the annealed primers using the synthesizing reagents to generate at least one copy of the target nucleic acids (see Fig. 1, col. 2, lines 52-56, and col. 6, lines 17-21)

(d) adding a non-inherent UDT to the extended primers (see Figure 1, column 2, lines 58-65, and column 6, lines 25-32).

Regarding claims 252 and 253, Lin teaches that the library of targets is isolated from a biological source (column 6, lines 15-17) or comprises complete or partial copies of nucleic acids isolated from a biological source (see Figure 1, step e and column 6, lines 35-55, where complementary copies of the nucleic acids isolated from the biological source are used as the library of targets from which a complementary copy is synthesized).

Regarding claims 254-258, Lin teaches that the homopolymeric sequences, specifically poly A sequences, are present prior to the isolation of the library of targets from the biological source (see Figure 1, step a and column 6, lines 15-25). Lin further teaches adding another homopolymeric sequence using TdT after the isolation of the targets from the biological sample and preparation of copies using the method of claim 251 (see Figure 1, step c and column 6, lines 25-32).

Regarding claim 261, Lin teaches that the synthesizing reagents comprise Taq polymerase (column 7, line 5).

Regarding claims 262 and 263, Lin teaches that the method of claim 251 further comprises providing:

(a) additional synthesizing reagents for synthesizing a complementary copy of the copy obtained in step (c) (see Figure 1, step c and column 6, lines 43-49)

(b) separating the nucleic acid target from the first nucleic acid copy (see Figure 1, step c and column 6, lines 43-49, where synthesis of the complementary copy by Pwo polymerase inherently results in separation of the target from the first copy)

(c) synthesizing the complementary copy using reverse primers complementary to sequences in the UDT (Figure 1, step c and column 6, lines 43-49, where the poly(dC) primer is taught).

Regarding claims 269-272, the forward and reverse primers taught by Lin comprise a production center since they contain T7, T3, or SP6 promoter sequences which function to produce multiple copies of the target nucleic acid sequence (see Figure 1 and column 6, lines 15-65; see also column 3, lines 28-31).

Regarding claim 273, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55)

(b) providing dNTPs and NTPs (column 6, lines 35-55)

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 275, Lin teaches that the transcription reaction is conducted in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Regarding claims 282 and 283, Lin teaches that the primer is attached to a solid matrix such as a glass slide (see column 5, lines 9-11, where the method is conducted using tissues in slides). In this embodiment of the method, the primer is indirectly attached to the solid matrix via hybridization with the immobilized target.

Regarding claims 284 and 285, Lin teaches that the homopolymeric segment is comprised of poly A, poly T, poly U, poly C or poly G (see Figure 1, column 3, lines 32-39, and column 6, lines 15-65).

Regarding claim 625, Lin teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(i) at least one nucleic acid target (col. 6, lines 10-17 and col. 2, lines 45-51; see also Figure 1, step a)

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct comprises one or more terminal nucleotides at the 3' end (see Figure 1, column 2, lines 52-56, and column 6, lines 17-21)

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (column 2, lines 52-55 and column 6, lines 15-24)

(b) annealing the primer or nucleic acid construct to the target nucleic acid (see Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21)

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (Figure 1, step b, column 2, lines 52-56, and column 6, lines 17-21).

Lin does not teach that the primers contain 3' terminal nucleotides that are substituted with nucleotide analogues containing a modification at the 2' position of the ribose ring as required by claims 251, 259, and 286. Lin also does not teach the use of chimeric primers as required by claim 260.

Laird teaches PCR amplification using modified primers (see abstract and paragraphs 12-18).

Regarding claims 251, 259, 286, and 625, Laird teaches conducting PCR using primers wherein 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-18). Laird teaches that the modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (paragraph 37).

Regarding claim 260, Laird teaches that the primers contain additional nucleotide analogues (paragraph 20).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Lin. An ordinary artisan would have been motivated to modify the primers taught by Lin to include the modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification (paragraph 37). Combining the

teachings of Lin and Laird would result in placement of at least one of the nucleotide analogs in the homopolymeric sequence comprising the 3' oligo(dT) tail of the primer taught by Lin. An ordinary artisan would have had a reasonable expectation of success in applying the teachings of Laird to the method taught by Lin, since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the methods of claims 251-264, 269-273, 275, 281-286, and 625 are *prima facie* obvious over Lin in view of Laird.

6. Claims 265-268 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Willis et al. (US 6,858,412; cited previously) and further in view of Moran et al. (Nucleic Acids Research (1996) 24(11): 2044-2052; cited previously).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Neither Lin nor Laird teaches including a terminator nucleotide in the TdT tailing reaction as required by claims 265-268.

Regarding claim 266, Lin teaches that the non-inherent UDT is added to a nucleic acid copy by providing TdT and non-terminator nucleotides (Figure 1, step c and column 6, lines 35-55).

Regarding claim 267, Lin teaches that the method of claim 266 further comprises:

(a) providing additional synthesizing reagents for the synthesis of a complementary copy of the nucleic acid copy (column 6, lines 35-55, where Pwo polymerase synthesizes a complementary copy of the UDT-containing copy)

(b) separating the target nucleic acid from the first nucleic acid copy (see Figure 1, step c and column 6, lines 35-55, where upon synthesis of the complementary copy, the target is inherently separated from the first copy)

(c) synthesizing the complementary copy (Figure 1, step c and column 6, lines 35-55).

Willis teaches amplification-based methods of nucleic acid analysis (see abstract and column 4, line 50 – column 5, line 15). Regarding claims 265, 266, and 268, Willis teaches the use of terminal transferase to add chain-terminating nucleotides, such as ddNTPs or acyclic nucleotides, to prevent extension or amplification (see column 26, lines 40-45).

Moran teaches that polymerase-mediated DNA and RNA synthesis reactions often produce molecules with non-homogenous or ragged 3' termini due to spurious template-independent addition of nucleotides by the polymerase (page 2044). Moran teaches that this "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." Regarding claims 265-267, Moran teaches that, "addition of a single non-coding nucleotide analogue to the 5' terminus of the template DNA strand can result in much more efficient and specific termination at the desired site (3'-end of the product). The use of such 'terminator' nucleotides results in the production of cleaner RNA and DNA oligonucleotide products, often in greater yields, and with more efficient use of nucleotides (page 2044, column 2 – page 2045, column 1)."

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Willis and Moran to the method resulting from the combined teachings of Lin and Laird. An ordinary artisan would have been motivated to include a terminator nucleotide, such as the dideoxy or acyclic nucleotides taught by Willis, in the terminal transferase tailing reaction taught by Lin, since Willis taught that these nucleotides prevented polymerase-mediated extension, and also since Moran taught that terminator nucleotides reduced template-independent addition of 3' terminal nucleotides by DNA and RNA polymerases (see column 46, lines 40-45 of Willis and pages 2044-2045 of Moran). An ordinary artisan would have been particularly motivated to minimize template-independent addition of nucleotides by the polymerase, since Moran taught that such addition "complicates purification, may interfere with subsequent reactions, such as ligation, and wastes nucleotide substrates (page 2044, column 2)." An ordinary artisan would have had a reasonable expectation of success in including dideoxy or acyclic nucleotides in the terminal transferase reaction taught by Lin, since Willis taught that terminal transferase could incorporate these nucleotides into nucleic acids (column 26, lines 40-45). Thus, the methods of claims 265-268 are *prima facie* obvious in view of the combined teachings of Lin, Laird, Moran, and Willis.

7. Claims 274 and 276 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Regarding claim 274, Lin teaches that the method of claim 271 further comprises:

(a) providing reagents for RNA transcription comprising RNA polymerase (see Figure 1, step d, column 2, line 66 – column 3, line 4, and column 6, lines 35-55)

(b) providing dNTPs and NTPs (column 6, lines 35-55)

(c) creating a transcript (column 6, lines 35-55 and Figure 1, step d).

Regarding claim 276, Lin teaches that the transcription reaction is conducted in the presence of labeled nucleotides to generate labeled transcription products (column 5, lines 19-23).

Lin does not teach inclusion of a mutated RNA polymerase for generation of a chimeric RNA/DNA transcript as required by claim 274.

Sousa teaches methods for synthesizing chimeric nucleic acid molecules using a mutant RNA polymerase (see abstract and column 4, line 53 – column 5, line 31).

Regarding claim 274, Sousa teaches providing reagents for RNA transcription comprising a mutated RNA polymerase, NTPs, & dNTPs and creating a chimeric DNA/RNA transcript (column 9, lines 41-46). Sousa further teaches that RNase A only cleaves RNA after a C or a U, and therefore, replacement of these rNMPs with dNMPs or other nucleotides resistant to nuclease cleavage would prevent this cleavage by RNase A (column 8, lines 55-67).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Sousa to the method resulting from the combined teachings of Lin and Laird. An ordinary artisan would have been motivated to utilize the mutant RNA polymerase taught by Sousa to generate chimeric DNA/RNA transcripts, since Sousa taught that such transcripts displayed improved resistance to ribonucleases (column 8, lines 55-67). An

ordinary artisan would have recognized that RNase degradation of the transcription product produced in step (d) of the method outlined in Figure 1 of Lin would be detrimental, since the method of Lin required a post-transcription PCR amplification step, and therefore, would have been motivated to minimize the possibility of such degradation by generating a chimeric DNA/RNA transcript as suggested by Sousa. Thus, the methods of claims 274 and 276 are *prima facie* obvious in view of the combined teachings of Lin, Laird, and Sousa.

8. Claims 277, 278, and 280 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; cited previously).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Regarding claim 277, although Lin teaches labeling nucleic acid amplification products at multiple stages of the method (transcription and TdT tailing – see column 5, lines 19-23), Lin does not teach including labeled nucleotides in the final RT-PCR amplification step used to generate a copy of the RNA transcription product as required by claim 277.

Regarding claims 278 and 280, Lin teaches labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Regarding claim 277, Steffens teaches including the labeled nucleotide in PCR reactions for incorporation into the resulting products (page 397, column 2).

Regarding claims 278 and 280, Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin and Laird. An ordinary artisan would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin and Laird, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, selection of a known material based on its suitability for the intended purpose is *prima facie* obvious. An ordinary artisan would also have been motivated to label nucleic acid products generated at any point in the method resulting from the combined teachings of Lin and Laird (*e.g.* the final RT-PCR step) in order to monitor the yield at each step of the process. An ordinary artisan would have been motivated to do so, since Lin taught labeling nucleic acid products produced at multiple steps of the method (see column 5, lines 19-23). As noted above, an ordinary artisan would have been motivated to utilize the fluorescently labeled nucleotide taught by Steffens to conduct this labeling step, since Steffens taught that the nucleotide permitted sensitive detection of labeled nucleic acids with minimal background. An ordinary artisan would have had a reasonable expectation of success in using the fluorescently labeled nucleotide taught by Steffens, since Steffens expressly taught its use in PCR amplification (page 397, column 2). Thus, the methods of claims 277, 278, and 280 are *prima facie* obvious in view of the combined teachings of Lin, Laird, and Steffens.

9. Claim 279 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Sousa et al. (US 5,849,546; cited previously) and further in view of Steffens et al. (Genome Research (1995) 5: 393-399; cited previously).

The combined teachings of Lin, Laird, and Sousa result in the method of claims 274 and 276, as discussed above.

Regarding claim 279, Lin teaches labeling transcription products using labeled nucleotides (column 5, lines 19-23), but does not teach specific examples of labels.

Steffens teaches the use of a nucleotide labeled with an infrared fluorophore for detection of nucleic acids (see abstract). Steffens teaches including the labeled nucleotide in PCR and sequencing reactions for incorporation into the resulting products (pages 394-395). Steffens teaches that labeling nucleic acids with this nucleotide permits highly sensitive detection with minimal background (page 394, column 1).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to utilize the fluorescently labeled nucleotide taught by Steffens in the method resulting from the combined teachings of Lin, Laird, and Sousa. An ordinary artisan would have been motivated to utilize the nucleotide taught by Steffens to label transcription products generated by the method resulting from the combined teachings of Lin, Laird, and Sousa, since Steffens taught that labeling nucleic acids with this nucleotide permitted highly sensitive detection with minimal background (page 394, column 1). Also, as noted in MPEP 2144.07, selection of a known material based on its suitability for the intended purpose is *prima facie*

obvious. An ordinary artisan would have had a reasonable expectation of success in using the nucleotide taught by Steffens, since Sousa taught that the mutant RNA polymerase was capable of incorporating several different types of modified nucleotides (see column 9, lines 21-40). Thus, the method of claim 279 is *prima facie* obvious in view of the combined teachings of Lin, Laird, Sousa and Steffens.

10. Claim 287 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin et al. (US 6,197,554 B1; cited previously) in view of Laird et al. (EP 1201788; cited previously) and further in view of Borson et al. (PCR Methods and Applications (1992) 2: 144-148; cited previously).

The combined teachings of Lin and Laird result in the method of claims 251-264, 269-273, 275, 281-286, and 625, as discussed above.

Neither Lin nor Laird teach that at least one of the bases of the nucleotide analogs is different than the base comprising the homopolymeric segment as required by claim 287.

Borson teaches a method for synthesizing cDNA molecules from mRNA templates using a primer comprising an oligo(dT) portion and two additional 3' terminal nucleotides that are different from those in the homopolymeric tail of the primer and template molecules (see page 144, column 3). Borson teaches that inclusion of these two 3' terminal nucleotides "locks the primer at the beginning of the polyadenylation signal rather than at random points along a potentially lengthy poly(A) tail (page 144, column 3)." Borson further teaches that this "lock-docking" capability of the primer results in improved homogeneity of the resulting products (pages 144 and 146).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Borson to the method resulting from the combined teachings of Lin and Laird. An ordinary artisan would have been motivated to further include additional 3' terminal nucleotides that were different from the homopolymeric sequence in the oligo(dT) primers taught by Lin since Borson taught that these additional 3' terminal nucleotides locked the primer at the beginning of the poly(A) tail, thereby improving the homogeneity of the resulting cDNA population (see pages 144-146, cited above). An ordinary artisan would also have been motivated to substitute these 3' terminal nucleotides with nucleotide analogues containing modifications at the 2' position of the ribose ring, since Laird taught that these modifications reduced nonspecific amplification (paragraph 37). An ordinary artisan would have had a reasonable expectation of success in applying the teachings of Borson to the method resulting from the combined teachings of Lin and Laird, since Borson taught that a degenerate set of "lock docking" primers could be used together to amplify cDNA from a diverse mRNA population (page 148). Thus the method of claim 287 is *prima facie* obvious in view of the combined teachings of Lin, Laird, and Borson.

11. Claim 625 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borson et al. (PCR Methods and Applications (1992) 2: 144-148; cited previously) in view of Laird et al. (EP 1201788; cited previously).

Borson teaches a method for synthesizing a copy of at least one nucleic acid target comprising:

(a) providing:

(i) at least one nucleic acid target (p. 144, col. 3, "mRNA isolation" section)

(ii) at least one primer or nucleic acid construct complementary to a poly A sequence in the nucleic acid target, wherein the primer or nucleic acid construct comprises one or more terminal nucleotides at the 3' end (p. 144, col. 3, "Primer Design for cDNA synthesis" section, where the lock-docking primer contains a poly(T) region that is complementary to a poly A sequence in the target and two 3' terminal nucleotides)

(iii) template-dependent synthesis reagents for the synthesis of a nucleic acid copy (p. 145, col. 1, "cDNA synthesis" section)

(b) annealing the primer or nucleic acid construct to the target nucleic acid (p. 145, col. 1, "cDNA synthesis" section)

(c) synthesizing a copy of the target nucleic acid using the target nucleic acid as a template and extending the primer or nucleic acid construct using the synthesizing reagents (p. 145, col. 1, "cDNA synthesis" section).

Borson does not teach that the 3' terminal nucleotide(s) of the primer contain 2' substitutions to the ribose ring.

Laird teaches PCR amplification using modified primers (see abstract and paragraphs 12-18). Regarding claim 625, Laird teaches conducting PCR using primers wherein 1-3 of the 3' terminal nucleotides are modified nucleotides selected from 2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides (paragraphs 12-13). Laird teaches that the modified primers increase the time required for initial primer extension, and thereby, reduce nonspecific amplification of the target nucleic acid (see abstract and paragraph 37).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Laird to the method taught by Borson. An ordinary artisan would have been motivated to modify the primer taught by Borson to include the modified nucleotides (2'-O-methyl-nucleotides, 2'-fluoro-nucleotides, and 2'-amino-nucleotides) taught by Laird at the 3' terminus, since Laird taught that the presence of these modified nucleotides at the 3' terminus of an amplification primer reduced nonspecific amplification (paragraph 37). An ordinary artisan would have had a reasonable expectation of success applying the teachings of Laird to the method taught by Borson, since Laird taught that the synthesis of primers containing the modified nucleotides was conducted using commercially available reagents and standard chemical synthesis methods known in the art (paragraphs 41-45). Thus, the method of claim 625 is *prima facie* obvious in view of the combined teachings of Borson and Laird.

Response to Arguments

12. Applicant's arguments filed on September 18, 2008 have been fully considered, but they were not persuasive.

Regarding the rejection of claims 251-264, 269-273, 275, 281-286, and 625 under 35 U.S.C. 103(a) as being unpatentable over Lin in view of Laird, Applicant first argues that the teachings of Laird are not applicable to the methods of Lin, because the method of Laird is directed to the specific exponential amplification of a small number of target nucleic acids, whereas the method of Lin is directed to the linear amplification of a library of different target nucleic acids (see page 15). Applicant argues that teachings of Laird limit the uses of the modified primers to exponential amplification methods, such as PCR, strand displacement

amplification, transcription-mediated amplification, and self-sustained sequence replication, and exclude the use of the modified primers in methods of linear, generalized amplification, such as the library amplification method taught by Lin (see pages 15-17).

This argument was not persuasive, because as discussed previously, Laird does not limit the use of the modified primers to any particular type of amplification method, stating, "However, the invention is not restricted to any particular amplification system. The use of the modified primers in other primer-based amplification methods in which primer-dimer or non-specific amplification product can be formed is expected to be useful (page 7, paragraph 47)." Based on these teachings of Laird, an ordinary artisan would have been motivated to use the modified primers in any nucleic acid amplification reaction, such as the reverse transcription step conducted in the method of Lin, in order to reduce template-dependent non-specific amplification. Attention is also directed to sections 2123 and 2145 of the MPEP which state that patents are relevant for all that they would have suggested to the ordinary artisan and that the disclosure of alternative or preferred embodiments does not constitute a teaching away from other embodiments. In the instant case, as discussed above, Laird does not limit the use of the modified primers to the exponential amplification methods disclosed in the sections cited by Applicant, but rather states that the primers may be used in any amplification method where non-specific amplification and/or primer-dimer formation could be a problem (see page 7, paragraph 47). Since an ordinary artisan would have recognized that non-specific amplification should be minimized in any nucleic acid amplification process, he would have been motivated to use the modified primers of Laird in the method of Lin with a reasonable expectation of success. Furthermore, the teachings of Laird do not discredit, discourage, or disparage the use of the

modified primers in a generalized linear amplification method, such as the reverse transcription step conducted in the method of Lin, and therefore, the reference cannot be said to "teach away" from the claimed invention.

Applicant also argues that the teachings of Laird are directed to minimizing primer-dimer formation and non-specific amplification in exponential amplification methods designed to amplify specific targets, and therefore, they are not applicable or relevant to the single-primer reverse transcription step conducted in the library amplification method of Lin (see pages 17-18). In response to this argument that the Laird reference is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992).

In this case, the methods of Lin and Laird are both directed to the same problem, namely nucleic acid amplification. As discussed above, Laird does not limit the use of the modified primers to particular types of amplification reactions. Since mispriming by oligo(dT) (*i.e.* undesired non-specific amplification) was a known problem in reverse transcription reactions (see, for example page 1347 of Jones et al. (Genome Research (2001) 11: 1346-1352; newly cited) and pages 90-91 of Gregory et al. (Molecular and Biochemical Parasitology (1997) 87: 85-95; newly cited)), an ordinary artisan would have been motivated to utilize the modified primers of Laird in the reverse transcription step conducted in the method of Lin in order to reduce the possibility of generating 3' truncated cDNA molecules due to non-specific amplification from the oligo(dT) primer. Also, as discussed previously, Laird teaches that non-specific amplification

can occur during the preparation of the amplification reaction mixture (see paragraphs 4 and 28), and that use of the modified primers can reduce this undesirable reaction (paragraphs 12-17, 28, and 47). Based on these teachings of Laird, an ordinary artisan also would have been motivated to use the modified primers in the method of Lin in order to minimize the possibility of non-specific amplification occurring during the setup of the reverse transcription reactions. Thus, the teachings of Laird are reasonably pertinent to the method of Lin and an ordinary artisan would have been motivated to apply them with a reasonable expectation of success.

Lastly, attention is directed to Dystar v. Patrick Co., 80 USPQ 2d 1641, 1651 (Fed. Cir. 2006), where the court stated:

> Indeed we have repeatedly held that an implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the "improvement" is technology-independent and the combination of references results in a product or process that is more desirable, for example, because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunites by improving a product or process is universal - and even common-sensical – we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references.

The Dystar court clarifies that motivation exists when the improvement made results in a more desirable product or process, and the issue devolves to whether the ordinary artisan possesses the knowledge rendering him capable of combining the references. Here, the ordinary practitioner is a PhD with years of experience. As noted in Dystar, "If, however, as we have held as a matter of law, the level of skill is that of a dyeing process designer, then one can assume comfortably that such an artisan will draw ideas from chemistry and systems engineering – without being told to do so (Dystar at page 1653)." In the instant case, an ordinary artisan reading the Lin and Laird references, would have recognized that the modified primers of Laird

would be useful for reducing non-specific amplification in any template-dependent amplification process, such as the reverse transcription step taught by Lin. An ordinary artisan also would have possessed the knowledge rendering him capable of obtaining the modified primers of Laird and using them in the method of Lin. Thus, an ordinary artisan would have been motivated to apply the teachings of Laird to the method of Lin with a reasonable expectation of success.

Since Applicant's arguments were not found persuasive, claims 251-264, 269-273, 275, 281-286, and 625 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Lin in view of Laird.

Applicant's arguments regarding the rejections of claims 265-268, 274, 276-280, and 287 made under 35 U.S.C. 103(a) have been fully considered, but they were not persuasive. Applicant argues that the primary combination of references (Lin & Laird) does not render the method of independent claim 251 obvious, and that the additional references cited do not address this deficiency in the primary combination of references (see pages 18-21). This argument was not persuasive, because as discussed above, the combined teachings of Lin and Laird render obvious the methods of claims 251-264, 269-273, 275, 281-286, and 625. Since Applicant's arguments were not found persuasive, the rejections of claims 265-268, 274, 276-280, and 287 have been maintained.

Applicant's arguments regarding the rejection of claim 625 under 35 U.S.C. 103(a) as being unpatentable over Borson in view of Laird have been fully considered, but they are not persuasive. Applicant argues that Borson and Laird are directed to exponential amplification methods designed to specifically amplify a small number of target sequences, and therefore, do not teach library amplification as required by claim 625 (see page 21). This argument was not

persuasive, because claim 625 does not require amplification of a library of nucleic acid sequences. This claim only requires amplification of at least one target nucleic acid present in a sample using a primer having the claimed features. It is noted that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Since Applicant's arguments were not persuasive, the rejection of claim 625 has been maintained.

Conclusion

13. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kenneth R Horlick/

Primary Examiner, Art Unit 1637